EULAR EVIDENCE BASED RECOMMENDATIONS FOR THE DIAGNOSIS OF HAND OSTEOARTHRITIS - REPORT OF A TASK FORCE OF THE EULAR STANDING COMMITTEE FOR INTERNATIONAL CLINICAL STUDIES INCLUDING THERAPEUTICS (ESCISIT)

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ABSTRACT

Objectives: To develop evidence based recommendations for the diagnosis of hand osteoarthritis (OA).

Methods: The multidisciplinary guideline development group comprised 16 rheumatologists, one physiatrist, one orthopaedic surgeon, one allied health professional, one radiologist and one evidence based medicine expert representing 15 different European countries. Ten key propositions regarding diagnosis were generated using a Delphi consensus approach. Research evidence was searched systematically for each recommendation. Whenever possible, the sensitivity, specificity and likelihood ratio (LR) were calculated. Relative risk and odds ratios were estimated for risk factors associated with hand OA. The quality of evidence was categorised according to the EULAR evidence hierarchy for diagnosis. The strength of recommendation was assessed using the EULAR visual analogue scale.

Results: Diagnostic topics included clinical manifestations (pain on usage, short duration of morning stiffness, target joints and pattern of distribution, Heberden's and Bouchard's nodes etc), radiographic features (joint space narrowing, osteophytes, subchondral sclerosis and cysts etc), subgroups (interphalangeal joint with/without nodes, thumb-base, erosive OA), differential diagnosis (RA, psoriatic arthritis, gout and haemochromatosis), laboratory tests (ESR, CRP and RF) and risk factors and co-morbidities (age, gender, BMI, other joint infections etc). The sensitivity, specificity and LR varied from test to test depending upon the cut-off level, gold standard and control subjects. Overall, there was no single

test which could be used to define hand OA on its own (LR <10). However, a composite of the tests greatly increased the chance of the diagnosis. The probability of a subject with hand OA was only 20% when Heberden's nodes alone were present, however the probability increased up to 88% when in addition the subject was over 40 years old, had a family history of the nodes and also had joint space narrowing on any finger joint. The strength of recommendation varied according to available research evidence and expert consensus.

Conclusion: Ten key recommendations for the diagnosis of hand OA were developed using a combination of research-based evidence and expert consensus. Clinical diagnosis of hand OA should be based on the assessment of a composite of the features.

INTRODUCTION

Hand osteoarthritis (OA) is a highly prevalent condition[1;2]. It occurs commonly, though not exclusively, in the context of generalised OA [3-5], and can result in considerable disability[6;7]. Although a number of criteria have been used to define hand OA (HOA) clinically, radiographically or epidemiologically[8-11], diagnosis and classification of HOA presents certain difficulties due to a number of issues. For example, the large number of joints that may be affected, presenting a large array of potential patterns of involvement; the nature of Heberden's and Bouchard's nodes and their relationship to underlying interphalangeal joint (IPJ) OA; the poor correlation at one joint between symptoms and structural changes of OA; apparent differentiation between thumb-base and IPJ OA in terms of risk factors and outcome; and lack of agreement concerning the nature and specificity of "erosive OA" as a discrete subset of HOA.

The EULAR OA Task Force has developed evidence-based recommendations for management of knee OA [12;13], hip OA [14] and more recently HOA [15]. At their last meeting in Zurich in March 2006 the Task Force agreed that issues relating to the diagnosis of HOA merit their own, separate consideration from those of management. Development of recommendations for the diagnosis of HOA should prove very useful, as have recent recommendations for the diagnosis of gout [16]. As before, it was agreed that recommendations should be developed using an evidence based format that involves both a systematic review of research evidence and expert consensus[17].

METHODS

Participants

A multidisciplinary guideline development group was commissioned by the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Twenty-one experts in the field of OA consisting of rheumatologists (16), physiatrist (1), orthopaedic surgeon (1), allied health professional (1), radiologist (1) and evidence-based medicine expert (1) representing 15 European countries agreed to take part in the study. The objectives were [1] to agree key propositions related to the diagnosis of HOA; [2] to identify and critically appraise research evidence for the diagnostic tests, risk factors and co-morbidities associated with HOA; and [3] to generate recommendations based on a combination of the best available evidence and expert opinion.

Experts' consensus

Each participant was asked to contribute independently up to 10 propositions related to key clinical aspects in the diagnosis of HOA. Consensus regarding the propositions was reached using the Delphi technique. The initial propositions were collated into a single list by a co-chair (MD) who was not involved in the generation of propositions. Where necessary, the propositions were edited for English grammar and phrasing and similar, substantially overlapping propositions were combined. The edited list was then returned to the experts and they were asked to select the 10 most important from the list. Propositions were accepted if over 50% of the participants accepted them in any round, whereas propositions

receiving less than 15% votes were removed. Propositions receiving 15% to 50% votes entered the next Delphi round. The Delphi exercise was terminated when no further propositions had between 15% and 50% of votes. There was no limit to the number of final propositions selected.

Systematic literature search

A systematic search of the literature published between January 1945 and January 2006 was undertaken using MEDLINE (1966-), EMBASE (1980-), CINAHL (1980-), AMED (1985-) Science Citation Index through Web of Science (WOS) (1945-) and Cochrane Library databases (1996-). The search included both a general search and a proposition-specific search. The general search strategy consisted of three basic components: [1] HOA in whatever possible terms in the databases (Appendix 1); [2] types of research in the forms of systematic review/meta-analysis, cohort study, case-control study, cross-sectional study, economic evaluation (Appendix 2); and [3] diagnostic test/accuracy (Appendix 3). The first component search was combined with the second and third separately to retrieve potential studies in the literature for the diagnosis of hand OA. Summary results of the search were reported to the committee prior to the Delphi exercise.

After the Delphi exercise, the proposition-specific search was undertaken to identify evidence for each specific proposition. The search strategy included the terms for HOA and any possible terms for the specific component of each proposition. For example, "Heberden's nodes" and "Bouchard's nodes" were searched specifically for the proposition regarding these two clinical markers.

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The results of the general search and the proposition-specific search were then combined and duplications removed.   Medical subject heading search (MeSH), together with key word search was used whenever possible. All MeSH search terms were exploded. The reference lists within review or systematic reviews were examined and any additional studies meeting the inclusion criteria were included.

The search in the Cochrane Library included MeSH search of the Cochrane review, Abstracts of Quality Assessed Systematic Reviews, The Cochrane Controlled Trial Register, NHS Economic Evaluation Databases, Health Technology Assessment Database and NHS Economic Evaluation Bibliography Details Only.

Inclusion/exclusion criteria

Only studies concerning diagnosis of HOA were included. Studies for OA at several sites were included if data were presented separately for HOA. The main focus of interest was on tests (markers and features) for the purpose of HOA diagnosis. Studies in any form of design were included. Case reports, editorial or reviews were excluded, as were studies on healthy subjects or animals.

Level of evidence

Evidence was categorised according to the EULAR evidence hierarchy for diagnostic tests [16] (Table 2). Questions were answered using the best available evidence. For example, if a question could be answered by level Ia evidence (e.g., systematic review of cohort studies) then studies with a weaker design (e.g., cohort study - level IIa) were not reviewed. Results of the latest systematic

review were used if there was more than one systematic review for the same question. Results of different studies from same level of evidence were presented and statistical pooling was undertaken as appropriate[18].

Outcome measures

1. Gold standard

Gold standard is the diagnostic reference used to determine the validity (sensitivity and specificity) of a specific diagnostic test in a particular study. As there is no agreed gold standard for the diagnosis of HOA, established methods such as radiographic changes and expert diagnosis were used as a "diagnostic reference" or "gold standard" for HOA.

2. Validity

Diagnostic tests were assessed for validity and reliability. Validity was evaluated by sensitivity and specificity. Sensitivity is the proportion of true positives that are correctly identified by the test, whereas specificity is the proportion of true negatives that are correctly identified by the test [19]. The ideal test would have a value of 1 for both sensitivity and specificity, i.e., 100% sensitive and specific. However, in real life this is rarely possible and as sensitivity increases specificity often decreases. For example, increasing the diagnostic cut-off of joint space narrowing (JSN) grade would reduce the sensitivity but increase the specificity of the test in the detection of HOA. We therefore calculated the likelihood ratio (LR) (LR = sensitivity / (1-specificity)) to produce an overall trade-off index for both variables [20]. LR summarises how many times more (or less) likely patients with HOA are to be test positive than patients without the disease. A LR greater than

1 indicates that the test result is associated with the presence of HOA, whereas a LR less than 1 indicates that the test result is associated with absence of HOA. LRs above 10 or below 0.1 are considered to be strong evidence to respectively rule in or rule out a diagnosis in most circumstances [20]. In addition, LR allows users to predict the probability of having HOA for a patient, based on the risk of the source population. For continuous data, we used receiver operating curve (ROC) – the analysis for the area under the curve (AUC) between sensitivity (y axis) and 1-specificity (x axis) to determine the overall performance of a particular diagnostic test, given different cut-off indices to the test [21]. ROC =1 means 100% sensitive and specific. For example, ultrasound velocity (m/sec) was compared between HOA and normal control. Different cut-offs of this measure were given. Sensitivity and specificity were calculated for each cut-off point and a curve was drawn upon the derived sensitivities and specificities of all points. This brought about an ROC of 0.73 (ie. 73% of the maximum AUC), suggesting a good overall performance of this technique in the differentiation between HOA and normal joints [22].

2. Reliability

The reliability of a test was assessed using the kappa statistics (dichotomous data) and intra-class correlation analysis (continuous data) if repeat measures were available.

3. Relative risk and odds ratio

For risk factors and co-morbidities associated with the diagnosis of HOA, the relative risk (RR) and odds ratio (OR) were calculated. The RR was estimated

from cohort studies (for incident risk) or cross sectional studies (for prevalent risk), whereas the OR was calculated from case control studies [23]. Both present how many times more likely (or less likely) subjects who are exposed to the risk factor are to have HOA than those who are not exposed to the same risk factor. RR/OR = 1 indicates no relationship, whereas RR/OR >1 or <1 indicates positive or negative relationships between the risk factor and the disease.

4. Incremental cost-effectiveness ratio (ICER)

For economic evaluations, the ICER was calculated for the different costs between two diagnostic tests, divided by the different diagnostic values (sensitivity, specificity, or LR) between the two tests. In addition, the study design, comparator, perspective, time horizon, discounting, total costs and effectiveness were critically appraised.

Strength of recommendation

Following the literature search on each proposition and the initial drafting of the manuscript the Task Force met to discuss each proposition. At this stage, the wording (but not the content) of propositions could be adjusted to better clarify specific statements and to reduce any ambiguity if the majority of the Task Force agreed. The propositions were then ratified and a final adjusted manuscript was approved by all Task Force members.

The strength of recommendation (SOR) was graded using the EULAR visual analogue scale (VAS) [14]. Each participant was asked to score their SOR for each proposition using a 0-100 mm VAS. Participants were asked to determine their scores by taking into account both the research evidence

(sensitivity, specificity, LR and cost-effectiveness, if available) and their clinical

expertise (i.e. their clinical experience and opinion regarding logistics of the

diagnosis). The mean VAS and 95% CI were calculated.

Future research agenda

After the initial 10 propositions for diagnosis had been searched, reviewed and

discussed by the Task Force each participant was asked to propose 10 topics for

the future research agenda based on current available evidence and clinical

experience in the diagnosis of HOA. Similar, substantially overlapping

propositions were combined and then a Delphi approach was used to reach a

consensus on the 10 most important topics. The same criteria as those used to

select diagnostic propositions were employed (i.e., accepted: more than 50%

votes; removed: less than 15% votes; next round: 15% - 50% votes).

RESULTS

General literature search

The literature search yielded 6101 hits, including MEDLINE 2451, EMBASE

1860, CINAHL 243, AMED 55, WOS 757, and Cochrane 735. After deleting

duplications, 2,525 hits remained. Of them, only 108 studies met the inclusion

criteria. Whist over half of them (52%) were studies for risk factors or co-

morbidities, others were studies for clinical features (22%), radiographs (9%),

clinical & radiographic features (6%), other imaging (8%) (eg, ultrasound, MRI,

scintigraphy) and laboratory markers (3%) (eg, ESR and RF) (Figure 1).

Radiographs were the main "gold" standard used in these studies (39%). Other

"gold" standards included clinical (21%), clinical and radiographic (23%) and indeterminate (17%) (Figure 2). The majority of studies were cross-sectional (68/108), followed by case control (25/108), cohort (12/108) and systematic review (3/108) (Figure 3).

Expert's opinion approach

The experts were informed of the results of the general literature search and then the Delphi exercise was undertaken by email. The first round produced 184 propositions for diagnosis. After 3 anonymous Delphi rounds, 10 final propositions were agreed (Table 3).

Assessment of propositions

The proposition-specific search was then undertaken and the results were merged with the results from the general search to form the basis of evidence for the evaluation of each proposition or tests within each proposition. The following propositions are grouped by topic (risk factors, clinical manifestation, subsets, differential diagnosis, imaging and laboratory investigation) with no weighting according to order.

1.   Risk factors for HOA include female sex, increasing age over 40, menopausal status, family history, obesity, higher bone density, greater forearm muscle strength, joint laxity, prior hand injury and occupation or recreation-related usage.

Strength of recommendation (95%CI): 69 (54, 84)

The gender difference for HOA has been systematically reviewed, examining 2 incidence and 14 prevalence studies. Women have a slightly greater prevalent

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risk of HOA than men, with relative risks of 1.54 (95%CI 0.83, 2.86) for incidence

and 1.23 (95%CI 1.11, 1.34) for prevalence respectively [24]. When female gender

is used as a diagnostic criterion to differentiate HOA from other types of hand

arthritis the LR is not statistically significant (LR=0.94, 95%CI 0.80, 1.13)[8].

It is rare for HOA to develop before the age of 40, but after this age the

incidence increases dramatically, especially in women (Figure 6) [25]. Age has

been confirmed in many studies as one of the major risk factors for HOA [25-30] and

when a cut-off of 40 years is used as one of the diagnostic features for HOA it

has an LR of 3.73 (95%CI 2.69, 5.18) (Figure 4)[8]

Certain occupations such as cotton picking [31] increase the risk of HOA. A

systematic review of 11 case control and cross-sectional studies has confirmed

the importance of occupational hand usage. The risk of HOA was higher with

occupations requiring repetitive precision grip and forceful gripping, such as

cotton pickers, cooks, dentists, spinners and dockers. The risk was dose-

dependent, mainly targeting DIP and MCP joints but showing differential joint

distribution within the hand depending on the repetitive tasks involved [32].

Sex hormones may influence the development of HOA in women. Before

the age of 40 the prevalence and incidence of HOA are lower in women than

men, but after this age both become higher in women [25;33]. Because of the high

incidence of Heberden's nodes (a marker for risk of generalised OA) after this

age, the term "menopausal arthritis" is sometimes used [34]. The reduction in

estrogen due to the menopause may be associated with HOA.   However, this is

not supported by the evidence observed from the hormone replacement therapy

(HRT) studies, where the use of HRT was not associated with the reduced risk of HOA [35-38]. As these studies were observational studies, they may be confounded by the increased bone density (a potential risk factor for HOA) due to HRT [39-43]. Therefore further well controlled prospective studies are required to establish whether oestrogen directly influences the risk of HOA.

Other well established risk factors for HOA include positive family history [8;44-47], obesity [8;28;43;48-52], and joint injury [43]. High forearm extensor muscle strength has also been suggested as a risk factor, presumably by increasing damaging mechanical forces in the hand [53] (Table 6).

In summary, major risk factors for HOA include age over 40 years (evidence IIa), female gender (Ib), positive family history (Ib), occupational usage (Ib), obesity (IIa) and finger joint injury (IIb). However, the diagnostic usefulness of these risk factors, singly or in combination, requires further study.

2.   Typical symptoms of HOA are pain on usage and only mild morning or inactivity stiffness affecting just one or a few joints at any one time; symptoms are often intermittent and target characteristic sites (DIPJs, PIPJs, thumb-base, index and middle MCPJs). With such typical features, a confident clinical diagnosis can be made in adults aged over 40.

Strength of recommendation (95%CI): 85 (77, 92)

Pain on usage has limited value for the diagnosis of HOA. Whilst this feature has excellent reliability (kappa 0.85 to 1.00) and specificity (0.94 to 0.99), the sensitivity is extremely low (0.01 to 0.10) and the LR ranges from 0.50 to 5.50 (Table 4) [11]. However, limited duration of localised morning or inactivity stiffness

is more specific to HOA than inflammatory arthritis (eg, on average, 22 minutes for hand OA versus 58 minutes for RA) [54]. By contrast, the presence of uncharacterised hand pain (unspecified in terms of location, relationship to usage or rest) is not specific to HOA [7]. Pain in HOA is variable in severity and often varies with time [6.]

HOA mainly targets DIP, PIP and thumb base joints [8;26;27;29;30;55;56]. The prevalence of symptomatic HOA (symptoms plus radiographic Kellgren and Lawrence grade ≥2) is highest with DIP, followed by thumb base, PIP and MCP joints [29;30;55;57]. The distribution of HOA clusters by row and by ray [55;58]. The presence of OA at one finger joint is associated with OA at other finger joints in the same row (OR 6.4, 95%CI 4.3, 9.4 in men and 5.2, 95%CI 4.5, 6.0 in women), and the same ray (OR=5.3, 95%CI 2.9, 10.0 in men and 3.3, 95% CI 2.6, 4.2 in women) of the same hand [55]. HOA also shows symmetry between hands [55;58-60], more so for radiographic joint space narrowing (JSN) than for osteophyte [60]. The presence of OA at a particular finger joint strongly associates with OA in the same joint of the opposite hand (OR=14.0, 95%CI 7.1, 27.8 in men and 29.8, 95%CI 19.2, 46.3 in women) [55].

In summary, pain on usage is not a specific clinical marker for HOA (evidence IIb). However, HOA strongly targets DIP, PIP and thumb base joints and the shorter duration of morning or inactivity stiffness plus clustering pattern and symmetric distribution may be useful to distinguish HOA from other forms of hand arthritis (evidence IIb).

3. ***Clinical hallmarks of HOA are Heberden's and Bouchard's nodes,***
and/or bony enlargement with or without deformity (e.g. lateral deviation of
IPJs, subluxation and adduction of thumb-base) affecting characteristic
target joints (DIPJs, PIPJs, thumb-base, and index and middle MCPJs).

Strength of recommendation (95%CI): 80 (69, 90)

Heberden's nodes (HN) and Bouchard's nodes (BN) associate with underlying

structural changes of HOA, especially osteophyte (OR=5.15, 95%CI 4.37, 6.08)

[61-63]. However, their sensitivity and specificity for HOA vary widely from 0.3 to 0.9

depending on the cut-off grade, gold standard and control subjects used. This in

part may reflect the common time lag between development of nodes and

appearance of structural x-ray change. Subsequently HN or BN have limited

value as a single diagnostic marker with an LR ranging from 0.50 to 5.50 and a

median of 1.46 (Table 4; Figure 4). However, nodes become more useful when

taken in combination with other HOA features (Figure 5). For example, the

probability of a subject with HOA is 20% when HN alone are considered, but this

increases to 88% when the subject is over 40 years old, has a family history of

HN and has joint space narrowing in any finger joint.

HN and BN may be useful for population screening for HOA. A self-

reported instrument for HN and BN has been developed and validated in a

random sample of 478 subjects aged 40-79 years [64]. Of 300 respondents, 139

were examined by a trained metrologist (the "gold standard"). Sensitivity of self-

reported nodes was 0.71 (95%CI 0.60, 0.83), specificity was 0.96 (0.92, 1.00)

and LR was 19.76 (6.43, 60.76) [64].

In brief, HN and BN are important clinical markers for diagnosis of HOA, especially when used in combination with other features of HOA (evidence Ib). Research evidence for the diagnostic values of other clinically-derived features and their distribution is lacking (evidence IV).

4.   *Functional impairment in hand OA may be as severe as in rheumatoid arthritis. Function should be carefully assessed and monitored using validated outcome measures.*

Strength of recommendation (95%CI): 57 (42, 73)

A number of studies have examined the functional impact of HOA [6;30;65-70]. Both pain [68] and radiographic changes [69] associate with impaired hand function in the setting of HOA. Functional impairment due to HOA may be similar in severity to that resulting from rheumatoid arthritis [71] (evidence IIb). Indeed, for many patients with HOA functional difficulty is their main presenting complaint. However, in one study the eventual functional outcome of fully established HOA (symptom onset ≥ 10 years before) was found to be relatively optimistic for nodal OA but not for erosive OA [70].

A number of validated instruments are available to assess hand function. These include the Health Assessment Questionnaire (HAQ) [72]; the Arthritis Hand Function Test (AHFT) [73]; the Arthritis Impact Measurement Scale 2 (AIMS2) [74]; and the Cochin [75] and Score for Assessment and quantification of Chronic Rheumatic Affections of the Hands (SACRAH) [71;76], the Functional Index for Osteoarthritis of the Hand (FIHOA) [65] and the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) [77]. A systematic review of these instruments has been

undertaken [78]. There is no universal instrument and the selection from these options is guided mainly by the clinical question (evidence Ib).

5.   *Patients with polyarticular HOA are at increased risk of knee OA, hip OA and OA at other common target sites (generalised OA) and should be assessed and examined accordingly.*

Strength of recommendation (95%CI): 77 (62, 92)

HOA may not only affect multiple joints within the hand, it also can occur as a component of "generalised" OA. Patients with HOA have increased risk of both knee OA (OR=3.0, 95%CI 1.2, 7.5) [79] and hip OA (OR=3.25, 95%CI 2.19, 4.84)[80] (evidence IIb). A recent population-based cohort study that followed 1235 subjects without hip and knee OA at baseline for over 6 years showed that the risk of developing knee OA or hip OA was 2 times greater (OR=2.1, 95%CI 1.3, 3.1) in those with HOA than in those without HOA at baseline [5] (evidence IIa).

OA of recognised target joints (DIP, PIP, CMC, knee, hip) correlates with each other which often appear in a cluster of 3 or more involved groups [27]. The strongest associations occur for DIP and PIP, followed by PIP and CMC, CMC and knee, PIP and knee, knee and hip and DIP and knee (Table 5). These data support the concept of "generalised OA" in which some individuals are at increased risk of multiple joint involvement by OA. Classification criteria for generalised versus focal OA have been proposed [4]. There is clear justification to include assessment of other target joints for OA for the purpose of diagnosis and treatment planning of HOA.

6.   Recognised subsets with different risk factors, associations and

outcomes (requiring different assessment and management) include IPJ

OA (with or without nodes), thumb-base OA, and erosive OA. Each may be

symptomatic or asymptomatic.

Strength of recommendation (95%CI): 68 (56, 79)

A number of studies have identified differences between erosive and non-erosive

OA (see next proposition for further details) (evidence IIa - IIb). Although HOA

clusters by joints, population-based cross-sectional studies have confirmed that

isolated thumb base OA is a common occurrence [81]. Apart from the location,

thumb base OA may associate with different risk factors from IPJ OA, although

both may share a similar genetic risk [44]. For example, hypermobility has been

reported as a risk factor for thumb-base OA [82] but a negative risk ("protective")

factor for IPJ OA [82;83].   Studies on functional impairment have not confirmed any

clear difference between thumb base OA and IPJ OA [84] (evidence IIb), however

the long-term functional outcome for erosive OA appears worse than for nodal

OA [70].   Further research is required to define how clearly such subsets are

delineated.

7.   Erosive hand OA targets IPJs and shows radiographic subchondral

erosion which may progress to marked bone and cartilage attrition,

instability and bony ankylosis. Typically it has an abrupt onset; marked

pain and functional impairment; inflammatory symptoms and signs

(stiffness, soft tissue swelling, erythema, paraesthesiae); mildly elevated

CRP; and a worse outcome than non-erosive IPJ OA.

An age and gender matched case control study has compared radiographic features of erosive OA (n=33) and nodal OA (n=33) using summated scores for individual OA features (JSN, osteophyte, subchondral sclerosis, subchondral cysts) at different joint sites. Erosive OA had significantly higher scores than nodal OA at DIP, PIP and thumb IP joints, but not at MCP and CMC joints, supporting the selective targeting of IP joints by erosive OA [85]. This observation is supported by two cohort studies which further suggest that this pattern is associated with a worse radiographic outcome [86;87]. In two case control studies subchondral erosion, bony collapse and ankylosis of IP joints appeared specific to erosive OA [85;88]. In one case control study comparing observed hand function in patients with established nodal HOA (n = 57), patients with established erosive OA (n = 10) and normal non-OA subjects (n = 52), hand function was worse in the erosive OA patients [70].

One case control study has examined differences in capillaroscopic abnormalities between erosive OA and nodal OA. Although some statistically significant differences were found for frequency of microhaemorrhages, tortuous capillary loops and shortened loops, they did not prove very discriminatory with LRs of 2.19 (95%CI 0.62, 7.78), 1.21 (1.85, 1.74) and 3.29 (1.34, 8.07) respectively [89].

Serum CRP levels have been measured in a case control study examining 67 patients with erosive OA and 31 patients with non-erosive OA. CRP levels were higher in the erosive OA group and the observed correlations between CRP

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level, radiographic severity scores and number of joints involved supported CRP as an indicator of disease activity [90].   No differences in serum levels of type II cartilage biomarkers (Col2-3/4C, C2C, and CS846 epitope) were demonstrated between 30 erosive OA patients and 29 patients with non-erosive HOA [91].

Ultrasound has been investigated as a means to differentiate erosive OA, non-erosive HOA and normal joints. One case control study (n=60) including 20 subjects per group found ultrasound to differentiate erosive OA from normal (ROC 0.75 - ROC 1 means 100% sensitive and specific) and non-erosive HOA from normal (ROC 0.73), but not erosive OA from non-erosive HOA (ROC: not reported)[22].

In summary, erosive OA appears to be a specific subgroup of HOA with worse clinical and structural outcomes. It targets mainly the IP joints with structural changes which are often severe (subchondral erosion, ankylosis) and inflammation (elevated CRP) (evidence IIa - IIb).

8.   The differential diagnosis for HOA is wide. The commonest conditions to consider are psoriatic arthritis (which may target DIPJs or affect just one ray); rheumatoid arthritis (mainly targeting MCPJs, PIPJs , wrists); gout (which may superimpose on pre-existing HOA) and haemochromatosis (mainly targeting MCPJs, wrists).

Strength of recommendation (95%CI): 81 (73, 89)

The differential diagnosis between hand OA and other arthropathy may be based on clinical manifestations (eg, age, gender, onset and progression of symptoms, degree of stiffness, joints involved (Figure 7), presence of HN/BN, examination

findings of synovitis and/or damage), radiographic changes (Figure 8) and laboratory tests.   However, as for diagnosis, a single criterion on its own has limited sensitivity and specificity (Figure 5). For example, although DIP joints are mainly targeted by OA they can also be involved in rheumatoid arthritis (RA) [9]; inflammatory symptoms and signs and elevation of CRP may occur with both erosive OA and RA; radiographic changes of HOA and calcium pyrophosphate dehydrate deposition disease (CPPD) associated arthritis are extremely similar [92] and HOA may coexist with CPPD [93;94], gout or RA.

A composite of multiple features is more useful, such as age, female gender, joint distribution, bone swelling (not soft tissue) and radiographic changes. Laboratory tests, although non-specific, may assist in this, for example strongly positive RF is supportive of RA (Table 4) and elevated urate may support gout. However, some individual features do have high specificity (eg non-proliferative marginal erosion for RA, urate crystals for gout).

In brief, differential diagnosis of HOA and other types of hand arthritis depends largely on the use of a composite of features (evidence Ib). Certain features for individual diseases may be useful for specific cases (IIb).

9. **Plain radiographs provide the gold standard for morphological assessment of HOA. A postero-anterior radiograph of both hands on a single film/field of view is adequate for diagnosis. Classical features are joint space narrowing, osteophyte, subchondral bone sclerosis and subchondral cyst; subchondral erosion occurs in erosive hand OA. Further imaging modalities are seldom indicated for diagnosis.**

Strength of recommendation (95%CI): 87 (81, 93)

Structural changes on plain radiographs have been used by the majority of studies as the "gold" standard for the assessment of a diagnostic test [95-98](Figure 2). The validity of radiographic change itself has been examined in two case control studies in which the clinical diagnosis was used as the "gold standard" [8;9]. Classical radiographic features such as JSN and osteophyte are sensitive (sensitivity 0.75-1.0) but not specific (specificity 0.18-0.71), resulting in small LRs (pooled LR1.60, 95%CI 1.29, 1.99 for JSN and 1.61, 95%CI 1.12, 2.33 for osteophyte) (Table 4 and Figure 4). Thus, a single feature (eg, JSN or osteophyte) is less valuable for the diagnosis than a composite of 2 or more features (Figure 5).

Clearly the reliability of any test is an important consideration and several studies have examined specifically the reproducibility of radiographic OA scores [99-101]. The intra-reader reliability (kappa) of radiographic features for HOA ranges from 0.38 to 1.0 (kappa 0.56-1.00 for PIP joints, 0.38-0.87 for DIP joints and 0.58-0.69 for CMC-1 joints) and the inter-reader reliability (kappa) ranges from 0.52 to 0.92[100]. The latter may be improved by reader's experience (0.92-1.00)[99;101]. Reliability also varies according to the scale used, eg, the Verbruggen and Kellgren and Lawrence scale may have better reproducibility than global and Kallman scales[101].

The value of MRI in early diagnosis has been examined in a case control setting where chronic OA (symptoms >12 months, n=14), early OA (symptoms ≤12 months, n=16), "latent" OA (asymptomatic, no history of pain and swelling in

a patient with HOA, n=14) and normal controls (n=18) were compared [97].
Abnormalities in soft tissues and bones were observed in all the HOA categories
compared to controls, with periarticular changes being particularly striking in the
least affected and latent joints. The suggestion from this study that MRI may help
identify early HOA when radiographs are normal requires confirmation.

Scintigraphy has been examined as a means of early diagnosis of HOA in
a prospective cohort study in which 30 subjects with normal radiographs but
abnormal scintigraphy at baseline were followed for one year. According to the
clinical and/or radiographic criteria of HOA the sensitivity of scintigraphy was
98.2%, specificity was 57.1%, and the LR was 2.29 [95]. In addition scintigraphy
has been used to predict the progression of HOA in a 5-year cohort study, in
which moderate sensitivity (0.53, 95%CI 0.42, 0.63) and good specificity (0.93,
95%CI 0.92, 0.94) were observed (Table 4)[102].

In summary, the plain radiograph is the validated principle imaging
technique to examine morphological changes of HOA (evidence IIb). Diagnosis
based on a single radiographic feature (eg, JSN or osteophyte) has limited value,
whereas presence of multiple features, especially a composite of clinical and
radiographic changes, dramatically improves diagnostic certainty (evidence Ib).
Other imaging techniques are relatively understudied and their clinical
applications have yet to be determined.

**10.   Blood tests are not required for diagnosis of HOA but may be
required to exclude co-existent disease. In a patient with HOA who has
marked inflammatory symptoms and/or signs, especially involving atypical**

sites, blood tests should be undertaken to screen for additional

inflammatory arthritides.

Strength of recommendation (95%CI): 78 (63, 92)

Unlike RA or other forms of inflammatory arthritis, inflammatory markers are not

usually elevated in HOA. It is well documented that ESR, RF (evidence Ib) and

CRP (evidence IIb) are usually normal/negative or only mildly elevated/positive

in non-erosive OA (Table 4)[8;9;54;89;103]. Therefore more pronounced abnormalities

should lead to a search for an alternative explanation. However, as discussed, a

single blood test may be unable to differentiate between erosive OA and RA, or

confirm the presence of coexisting inflammatory arthropathy. It is necessary to

consider other clinical and investigational features which are more characteristic

and/or specific for each condition (eg, proliferative or non-proliferative marginal

erosions in psoriatic and rheumatoid arthritis respectively, elevated serum uric

acid and urate crystal identification on aspiration of a joint or tophus in gout).

Future research agenda

After 3 Delphi rounds 9 propositions for future research were developed (Table

7).

DISCUSSION

To our knowledge these are the first evidence based recommendation for the

diagnosis of HOA and the second EULAR recommendations to address

diagnostic issues in musculoskeletal disorders [16]. Until now the main reference

cited for diagnosis of HOA has been the ACR criteria for classification of HOA [8].

However, the current recommendations differ from the ACR criteria in several important ways. Firstly, the primary purpose of these recommendations is to provide guidance to assist clinicians to diagnose HOA, not to classify the disease for research or clinical trial purposes. The emphasis is on possible subsets and the differential diagnosis to be considered rather than on algorithms for classification of a single entity. Secondly, these are evidence-based recommendations in which research evidence has been summarised systematically from multiple studies undertaken in different countries. Therefore they have more generalisability than recommendations based on a single study population. Thirdly, clinical expertise from many countries across Europe has been incorporated within the recommendations, and importantly, the expertise has been synthesised systematically using a Delphi exercise. Therefore, the recommendations have less parochial and personal bias [104]. Finally, the strength of recommendation and confidence interval has been provided for each proposition, based both on the research evidence and clinical expertise. This is an important marker that reflects the magnitude of support for each statement and the confidence (variability of opinion) from the Task Force [104]. This information should help clinicians to gauge which statements have good general agreement and which are more open to personal interpretation.

Ten key recommendations have been generated. The topics are wide ranging and include risk factors for HOA, clinical manifestations, subsets, differential diagnosis, imaging and laboratory tests. The sensitivity and specificity for each recommended marker or test has been examined and the value of each

has been presented as a likelihood ratio to allow estimation of the likelihood of HOA given a positive test result. A diagnostic ladder has also been provided to show the probability of diagnosis of HOA when multiple features are considered. Clinicians may estimate the probability of HOA for any composite of the features that a patient may present in their daily practice based on the knowledge of the likelihood ratio for each feature (Table 3). Baye's formula or Fagan's nomogram may be used to estimate the probability [16]. Using such data it would be possible to develop a computer based risk prediction model for clinical use in which the proposed diagnostic features are listed and the probability of HOA calculated according to the features entered. Overall we found that the diagnosis of HOA cannot be determined with confidence using a single feature, even Heberden's nodes - the feature generally considered as the hallmark of HOA. A composite of several features is required to diagnose HOA.

There are several limitations to these recommendations. Firstly, although the evidence-based method is a widely accepted strategy to increase the power and generalisability of research evidence, it is still open to bias since the pooled studies may carry different confounding factors. Ideally evidence-based recommendations should reflect, and largely be derived, from the population in which they will be applied. Secondly, we only focused on key issues relating to diagnosis of HOA and did not attempt a comprehensive review of all reported aspects. Thirdly, generation of the recommendations was driven from a clinical perspective and the relevant research was examined later. Therefore we may have omitted important emerging information in the research literature that could

have potential diagnostic value. Such bias, however, should have been minimised by the general literature search and discussion undertaken prior to the Delphi exercise. Finally, the Delphi consensus approach has its own limitations. Although it is systematic it has restricted flexibility and as a result some propositions may overlap or appear repetitive or illogical. Therefore we discussed the final list of the Delphi results at our last face to face meeting to agree on necessary changes to improve clarity. During this, however, we did not delete or introduce content but did alter some phrasing and ordering of content.

In conclusion, ten key recommendations have been generated by the EULAR OA Task Force for diagnosis of HOA. The level of research evidence and strength of recommendation have been provided for each proposition. We hope that these recommendations will stimulate debate and increase interest in HOA and thereby lead to improved diagnosis and assessment of people with this highly prevalent condition.

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Table 1. Glossary

Term	Definition
Heberden & Bouchard nodes	Clinically defined postero-lateral firm/hard swellings. Heberden's – distal IPJ; Bouchard's – proximal IPJ. Nodes can occur with or without radiological and/or clinical abnormalities characteristics of HOA.
Nodal OA	Heberden and/or Bouchard's nodes plus underlying IPJ OA, defined clinically and/or radiologically.
Non-nodal OA	IPJ OA, defined clinical and/or radiographically, without nodes
Erosive OA	Subset of HOA defined radiographically by subchondral erosion, cortical destruction and subsequent reparative change which may include bony ankylosis.
Generalised OA	HOA plus OA at other sites.
Thumb base OA	First CMCJ with or without STJOA
Gold standard	The diagnostic reference used for a particular study

OA= osteoarthritis; IPJ = interphalangeal joint; CMCJ = carpometacarpal joint; STJ = scapho-trapezioid joint

Table 2. EULAR evidence hierarchy for diagnosis based on study design[16]

Ia – meta-analysis of cohort studies

Ib – meta-analysis of case control studies

IIa – cohort studies

IIb – case control/cross sectional comparative studies

III – non-comparative descriptive studies

IV – expert opinion

Table 3. Propositions and strength of recommendation (SOR) – order according to topic (risk factors, clinical, subsets, differential diagnosis, images and laboratory tests)

No.	Proposition	LoE	SOR (95%CI)
1	Risk factors for HOA include female sex, increasing age over 40, menopausal status, family history, obesity, higher bone density, greater forearm muscle strength, joint laxity, prior hand injury and occupation or recreation-related usage.	Ib - IIb	69 (54, 84)
2	Typical symptoms of HOA are pain on usage and only mild morning or inactivity stiffness affecting just one or a few joints at any one time; symptoms are often intermittent and target characteristic sites (DIPJs, PIPJs, thumb-base, index and middle MCPJs). With such typical features, a confident clinical diagnosis can be made in adults aged over 40.	IIb	85 (77, 92)
3	Clinical hallmarks of HOA are Heberden's and Bouchard's nodes, and/or bony enlargement with or without deformity (e.g. lateral deviation of IPJs, subluxation and adduction of thumb-base) affecting characteristic target joints (DIPJs, PIPJs, thumb-base, and index and middle MCPJs).	Ib - IV	80 (69, 90)
4	Functional impairment in hand OA may be as severe as in rheumatoid arthritis. Function should be carefully assessed and monitored using validated outcome measures.	IIb	57 (42, 73)
5	Patients with polyarticular HOA are at increased risk of knee OA, hip OA and OA at other common target sites (generalised OA) and should be assessed and examined accordingly.	IIa - IIb	77 (62, 92)
6	Recognised subsets with different risk factors, associations and outcomes (requiring different assessment and management) include IPJ OA (with or without nodes), thumb-base OA, and erosive OA. Each may be symptomatic or asymptomatic.	IIa - IIb	68 (56, 79)
7	Erosive hand OA targets IPJs and shows radiographic subchondral erosion which may progress to marked bone and cartilage attrition, instability and bony ankylosis. Typically it has an abrupt onset; marked pain and functional impairment; inflammatory symptoms and signs (stiffness, soft tissue swelling, erythema, paraesthesiae); mildly elevated CRP; and a worse outcome than non-erosive IPJ OA.	IIa - IIb	87 (81, 93)
8	The differential diagnosis for HOA is wide. The commonest conditions to consider are psoriatic arthritis (which may target DIPJs or affect just one ray); rheumatoid arthritis (mainly targeting MCPJs, PIPJs , wrists); gout (which may superimpose on pre-existing HOA) and haemochromatosis (mainly targeting MCPJs, wrists).	Ib - IIb	81 (73, 89)
9	Plain radiographs provide the gold standard for morphological assessment of HOA. A postero-anterior radiograph of both hands on a single film/field of view is adequate for diagnosis. Classical features are joint space narrowing, osteophyte, subchondral bone sclerosis and subchondral cyst; subchondral erosion occurs in erosive hand OA. Further imaging modalities are seldom indicated for diagnosis [figure].	Ib - IIb	87 (81, 93)
10	Blood tests are not required for diagnosis of HOA but may be required to exclude co-existent disease. In a patient with HOA who has marked inflammatory symptoms and/or signs, especially involving atypical sites, blood tests should be undertaken to screen for additional inflammatory arthritides.	Ib - IIb	78 (63, 92)

LoE: level of evidence (see Table 2 for further details), presented in range upon components assessed; SOR: strength of recommendation on visual analogue scale (0-100 mm, 0=not recommended at all, 100 = fully recommended); CI: confidence interval.

Table 4 Tests and markers used in the diagnosis of hand osteoarthritis

Diagnostic test	Study design	N	Gold standard	Sensitivity (95%CI)	Specificity (95%CI)	LR (95%CI)	Reliability (Kappa/ICC)	Ref
General								
Age >40 yrs	Case control (RA etc)	194	Clinical	1.00	0.73 (0.64, 0.82)	3.73 (2.69, 5.18)	-	[8]
Female sex	Case control (RA etc)	199	Clinical	0.71 (0.62, 0.79)	0.25 (0.17, 0.34)	0.94 (0.80, 1.13)	-	[8]
Family history of HN	Case control (RA etc)	197	Clinical	0.39 (0.29, 0.48)	0.83 (0.75, 0.90)	2.26 (1.37, 3.72)	-	[8]
Clinical								
Pain on usage	Cross-sectional	541	DIP, k/l≥2	0.01	0.99	1.00	0.85	[11]
			k/l≥2 + symptom	0.03	0.94	0.50		
			PIP, k/l≥2	0.05	0.99	5.00	1.00	[11]
			k/l≥2 + symptom	0.10	0.95	2.00		
			CMC, k/l≥2	0.22	0.96	5.50	1.00	[11]
			k/l≥2 + symptom	0.57	0.61	1.46		
Median						**1.46**		
HN (+/-)	Case control (RA etc)	199	Clinical	0.91 (0.85, 0.97)	0.67 (0.57, 0.76)	2.73 (2.05, 3.63)	-	[8]
HN (≥1)	Case control	6590 joints	OST ≥1	0.41 (0.38, 0.44)	0.92 (0.91, 0.93)	5.13 (4.57, 5.76)	0.78	[62]
HN (≥1)	Case control	3730 joints	OST ≥1	0.83 (0.82, 0.85)	0.51 (0.48, 0.55)	1.72 (1.61, 1.83)	0.6-0.8	[63]
			JSN≥1	0.78 (0.76, 0.79)	0.34 (0.32, 0.37)	1.18 (1.13, 1.24)	0.6-0.8	[63]
HN (+/-)	Cross-sectional	541	k/l≥2	0.49	0.90	4.90	0.68	[11]
			k/l≥2 + symptom	0.82	0.49	1.61		
Pooled						**2.30 (1.30, 4.07)**		
BN (+/-)	Case control	199	Clinical	0.81 (0.73, 0.88)	0.65 (0.55, 0.74)	2.29 (1.73, 3.04)	-	[8]
BN (+/-)	Case control	3730 joints	OST≥1	0.44 (0.40, 0.46)	0.80 (0.78, 0.81)	2.13 (1.92, 2.35)	0.5-0.7	[63]
BN (+/-)	Cross-sectional	541	k/l≥2	0.40	0.87	3.08	0.75	[11]
			k/l≥2 + symptom	0.75	0.49	1.47		
			JSN≥	0.37 (0.33, 0.40)	0.74 (0.73, 0.76)	1.42 (1.28, 1.59)	0.5-0.7	[63]
Pooled						**2.15 (1.95, 2.36)**		
Radiographic								
JSN	Case control	82	Clinical	0.83 (0.71, 0.94)	0.62 (0.47, 0.77)	2.17 (1.44, 3.27)	-	[9]
	Case control (RA)	140	Clinical	0.83 (0.71, 0.94)	0.40 (0.30, 0.50)	1.38 (1.11, 1.70)	-	[9]
JSN	Case control (RA etc)	199	Clinical	0.75 (0.67, 0.83)	0.54 (0.44, 0.63)	1.61 (1.27, 2.05)	-	[8]
Pooled						**1.60 (1.29, 1.99)**		
OST	Case control	82	Clinical	1.00	0.26 (0.13, 0.39)	1.35 (1.13, 1.62)	-	[9]
	Case control (RA)	140	Clinical	1.00	0.18 (0.10, 0.26	1.22 (1.11, 1.34)	-	[9]
OST	Case control (RA etc)	199	Clinical	0.83 (0.76, 0.90)	0.71 (0.62, 0.80)	2.83 (2.06, 3.90)	-	[8]
Pooled						**1.61 (1.12, 2.33)**		

		N	Reference	Sensitivity	Specificity	LR+	ICC	Ref
Cysts	Case control	82	Clinical	0.85 (0.74, 0.96)	0.81 (0.69, 0.92)	4.46 (2.36, 8.43)		[9]
	Case control (RA)	140	Clinical	0.85 (0.74, 0.96)	0.39 (0.29, 0.49)	1.39 (1.14, 1.71)	-	[9]
Pooled						**2.39 (0.76, 7.47)**		
Erosions	Case control (RA etc)	199	Clinical	0.43 (0.33, 0.53)	0.58 (0.48, 0.67)	1.01 (0.73, 1.40)	-	[8]
Malalignment	Case control (RA etc)	199	Clinical	0.51 (0.41, 0.61)	0.74 (0.65, 0.82)	1.94 (1.32, 2.84)	-	[8]
Other images								
Scintigraph	Cohort, 1 year	30	Clin/radiographic	0.98	0.57	2.29		[95]
Scintigraph (progression)	Cohort, 5 yr	2278 joints	Increase in OST, JSN or sclerosis	0.53 (0.42, 0.63)	0.93 (0.92, 0.94)	7.38 (5.75, 9.47)	0.84	[102]
Laboratory								
ESR < 20 mm/hr	Case control (RA etc)	155	Clinical	0.61 (0.49, 0.72)	0.80 (0.71, 0.88)	3.00 (1.90, 4.73)	-	[8]
ESR (-)	Case control	200	Clinical & x-ray	0.94 (0.89, 0.99)	0.81 (0.73, 0.89)	4.94 (3.29, 7.44)	-	[54]
Pooled						**3.89 (2.39, 6.34)**		
RF < 1:80	Case control (RA etc)	103	Clinical	0.86 (0.77, 0.96)	0.68 (0.56, 0.79)	2.67 (1.83, 3.90)	-	[8]
RF (-)	Case control (RA)	140	Clinical	1.00	0.81 (0.73, 0.89)	5.26 (3.51, 7.89)	-	[9]
Pooled						**3.73 (1.92, 7.25)**		

N = subjects or joints as specified; CI = confidence interval; LR = likelihood ratio; ICC = intra-class correlation; RA = rheumatoid arthritis; DIP = distal interphalangeal joint; PIP = proximal interphalangeal joint; CMC = carpometacarpal joint; k/l = Kellgren and Lawrence; HN = Heberden's nodes; BN = Bouchard's nodes; OST = osteophytes; JSN = joint space narrowing; ESR = erythrocyte sedimentation rate; RF = Rheumatoid factor

Table 5. Association of osteoarthritis between joints[27]

Index joints	Other joints	OR (95%CI)
DIP	PIP	31.7 (13.8, 72.5)
PIP	CMC	4.8 (2.7, 8.4)
CMC	Knee	2.4 (1.5, 4.4)
PIP	Knee	2.4 (1.3, 4.4)
Knee	Hip	2.1 (1.2, 3.4)
DIP	Knee	1.8 (1.1, 3.1)

OR = odds ratio; CI = confidence interval; DIP = distal interphalangeal; PIP = proximal interphalangeal; CMC = carpometacarpal.

Table 6. Risk factors and hand OA

Risk factor	Evidence[#]	Sample size	RR/OR (95%CI)	References
Female gender	Ib	14 studies	1.23 (1.11, 1.34)	[24]
Age, >40	IIb	194	3.68 (2.66, 5.09)	[8]
Family history, 1st degree etc	Ib	3 studies (n=4183)	2.57 (1.86, 3.55)	[8;44;45]
Obesity				
Relative weight index, per 20%↑	IIa	1276	1.69 (1.27, 2.18)	[49]
BMI, >29 vs. ≤24	IIb	78	8.3 (1.2, 56.5)	[52]
BMI, kg/m^2	IIb	82 pairs	1.30 (1.06, 1.59)	[50]
BMI, kg/m^2	IIb	573 women	1.03 (0.96, 1.11)	[43]
BMD, dg/cm^2	IIb	573 women	1.11 (0.61, 2.02) kl≥2 1.61 (1.27, 2.07) kl=4	[43]
Grip strength, 3rd tertile	IIa	756	2.8 (1.2, 6.7)	[53]
History of hand injury	IIb	573 women	3.64 (1.34, 9.88)	[43]

# please see table 2 for further description
RR = relative risk; OR = odds ratio; CI = confidence interval; BMI = body mass index

Table 7. Future research agenda for diagnosis of hand OA

No.	Proposition
1	The relative utility of imaging techniques (plain x-rays, MRI, ultrasonography, scintigraphy) in both early diagnosis and evaluation of progression of the HOA sub-sets needs to be determined.
2	Risk factors both for development and long term clinical outcome of the different sub-sets of HOA need to be determined.
3	Potential biomarkers of bone, cartilage, synovium and inflammation should be examined in HOA subsets for utility in terms of early diagnosis, assessment of disease activity and prediction of outcome.
4	Diagnostic and classification criteria to better define HOA and its sub-sets need to be developed and validated.
5	Further studies are required to confirm the associations between HOA and systemic risk factors such as menopausal state, bone density, obesity and metabolic syndrome, and to explain the mechanisms that underlie such associations.
6	The genetic factors that predispose to the different phenotypes of HOA need to be identified.
7	The population incidence and prevalence of HOA and its sub-types (both symptomatic and asymptomatic), standardised by age and gender, need to be confirmed.
8	Studies should be undertaken to determine whether erosive HOA is a discrete subset with specific risk factors and pathogenesis, or a subgroup of HOA with a worse outcome.
9	The association between the different HOA phenotypes and large joint OA (ie generalised OA) needs further examination.

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Figure legends

Figure 1. Diagnostic tests or elements examined in hand osteoarthritis

Figure 2. "Gold" standards used in the assessment of the diagnostic tests or
elements

Figure 3. Types of studies for the assessment of the diagnostic tests or elements

Figure 4. Likelihood ratio (LR) and 95%confidence interval (CI) of different
diagnostic makers or features (useful ruled in cut-off level LR=10)

Figure 5. Diagnostic ladder of hand OA (source population prevalence 10%)

Figure 6. Incidence of hand osteoarthritis by age and sex 1991-1992

Figure 7. Target sites of involvement with hand OA, erosive OA, psoriatic arthritis,
rheumatoid arthritis and haemochromatosis

Figure 8. Contrasting radiographic features at IPJs of: (A) OA - focal narrowing,
marginal osteophyte, sclerosis, osteochondral bodies; (B) erosive OA - subchondral
erosion; (C) psoriasis - proliferative marginal erosion, retained or increased bone
density; and (D) rheumatoid arthritis – non-proliferative marginal erosion, osteopenia.

Clinical
22%

Radiographic
9%

Clinical &
radiographic
6%

Other images
8%

Laboratory
3%

Risk factors /
comorbidities
52%

Systematic review 3
RCT/CT 0
Cohort 12
Case control 25
Cross sectional 68
Economic evaluation 0

Number of studies

Single test

Multiple tests
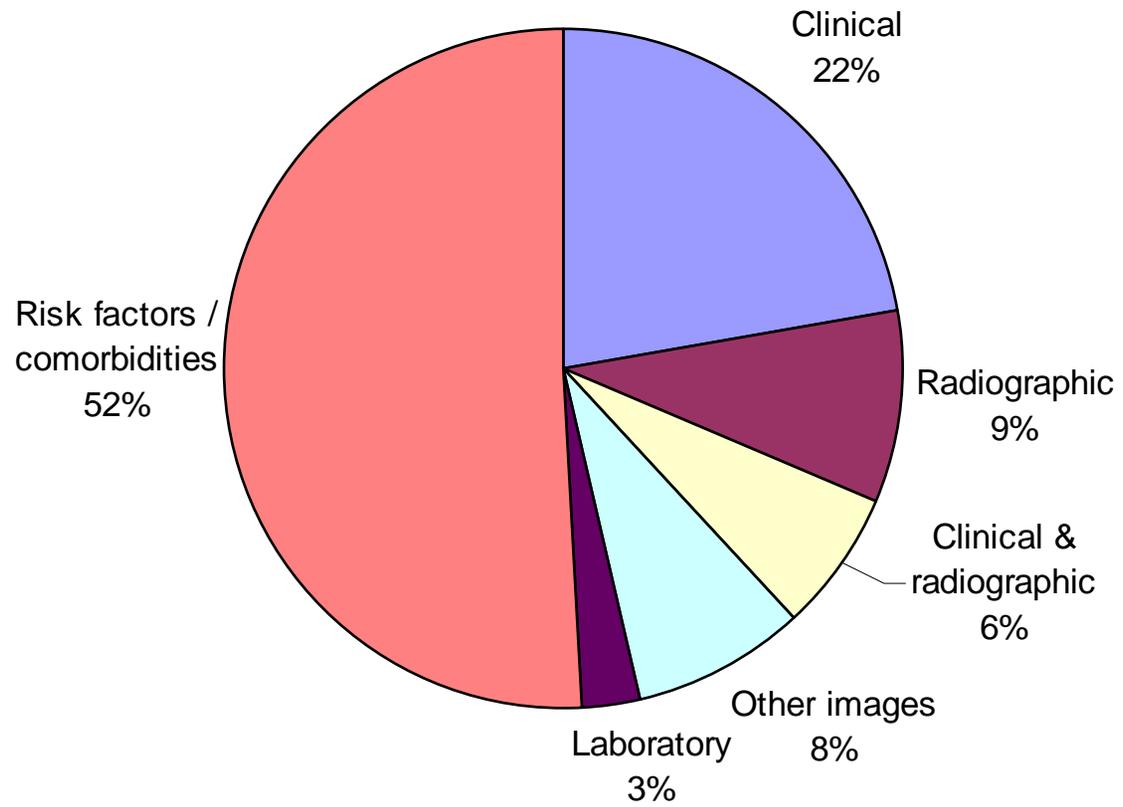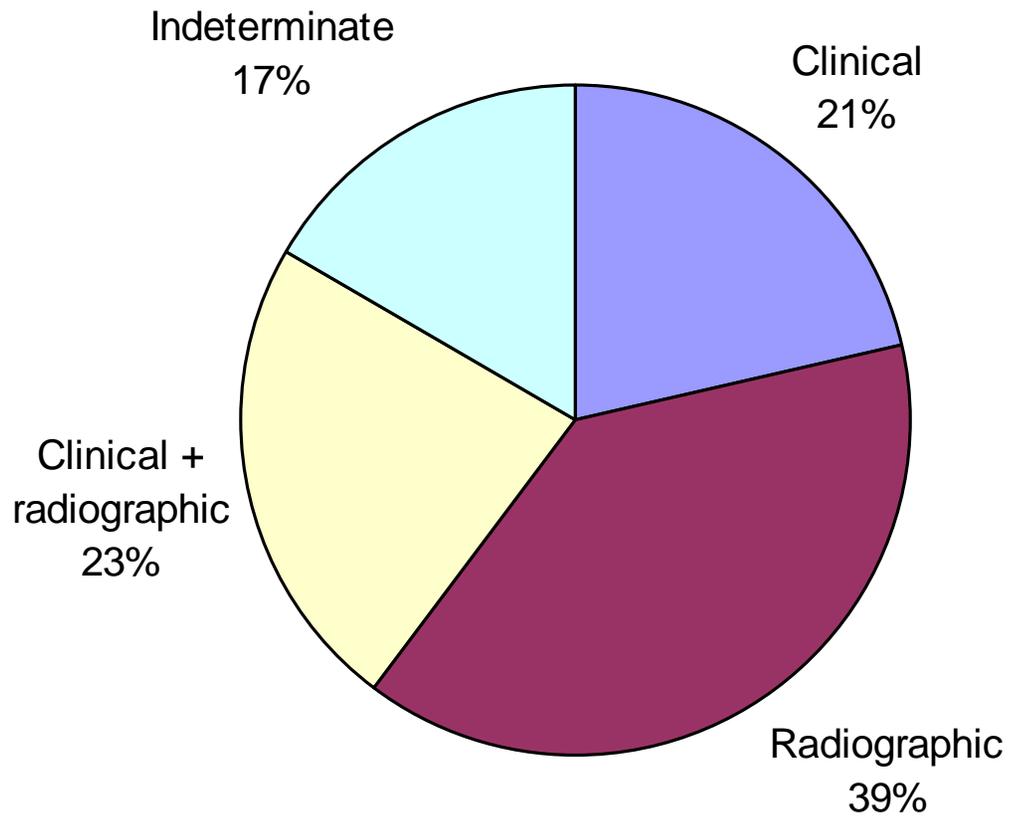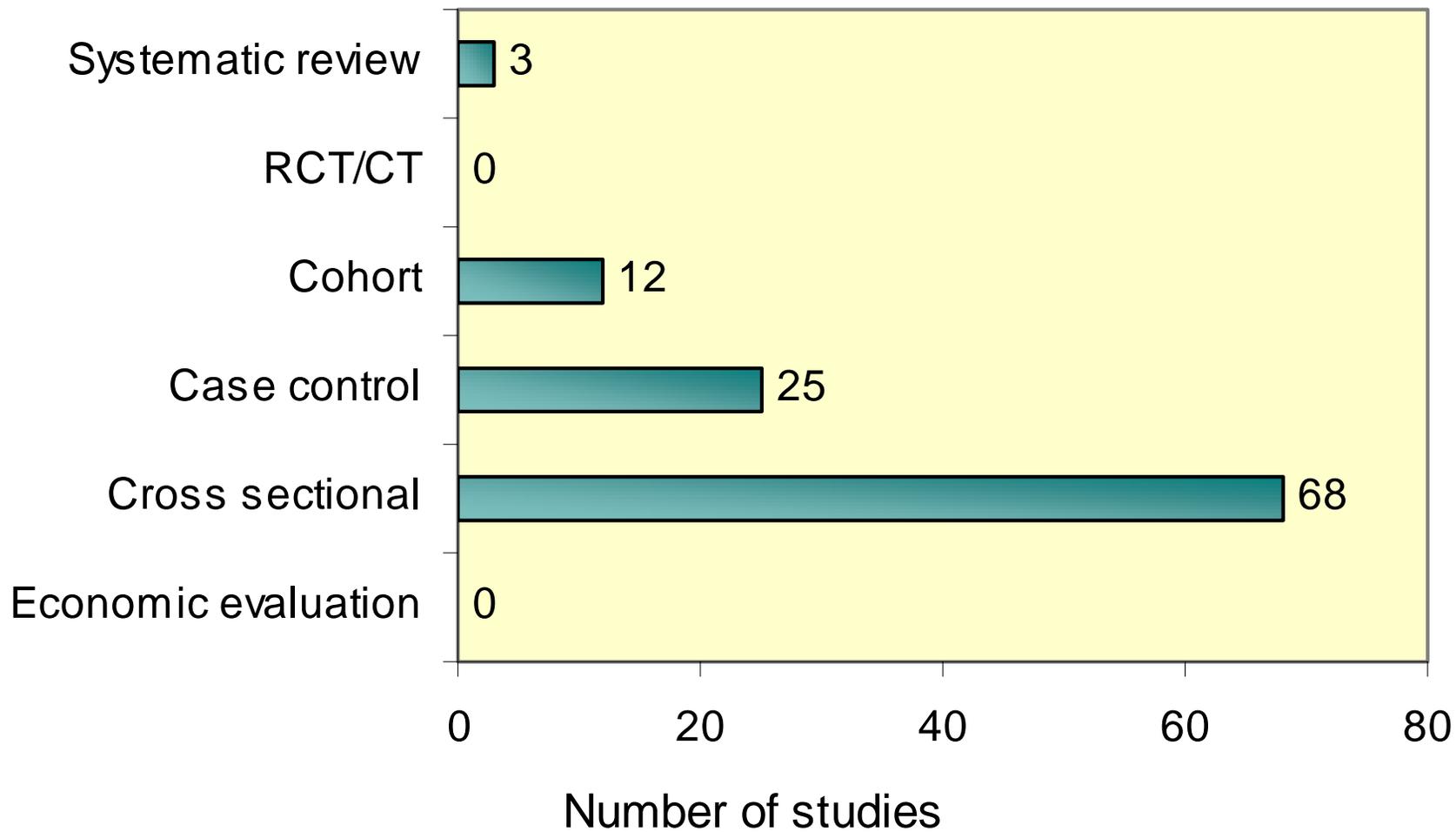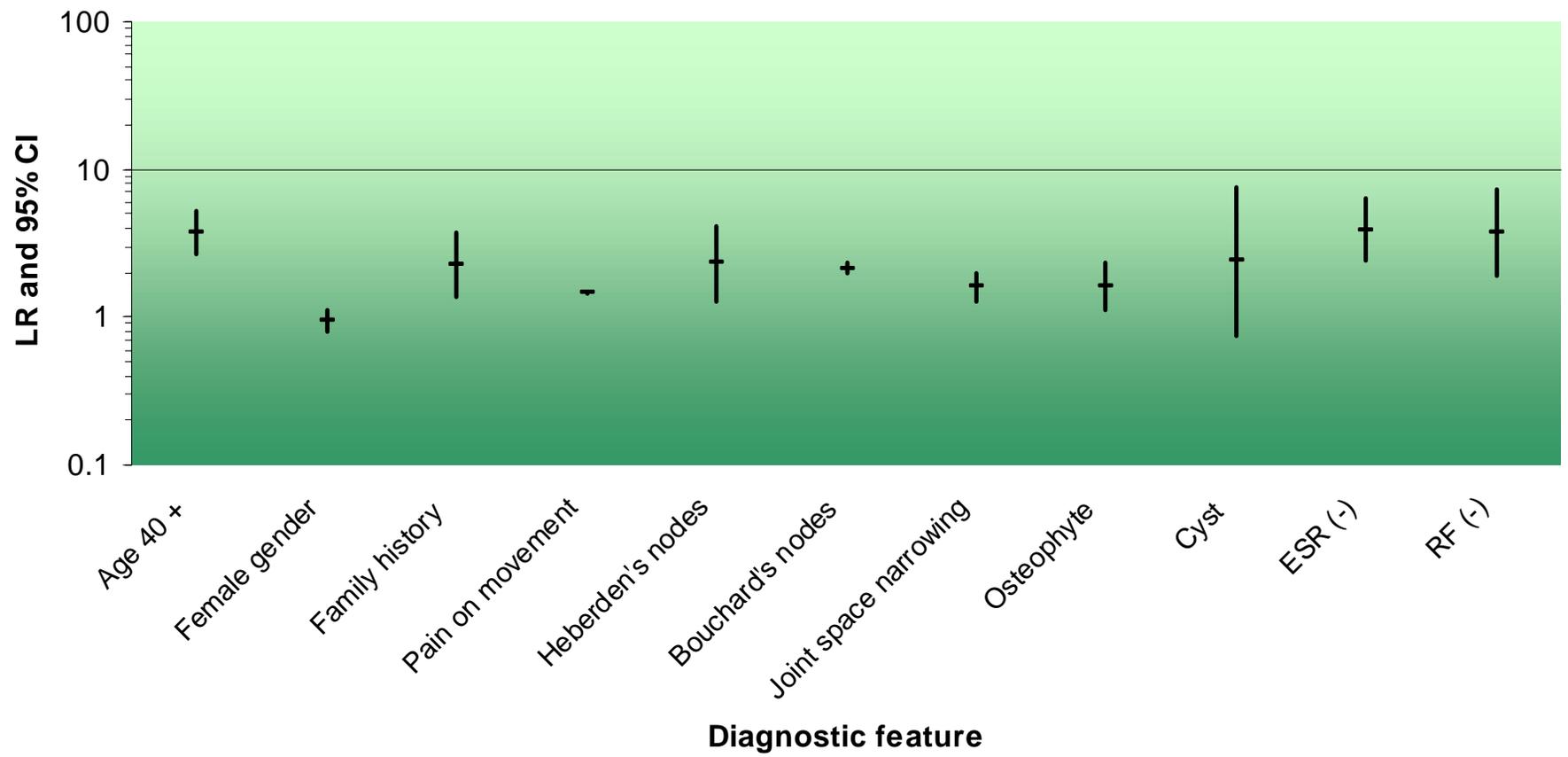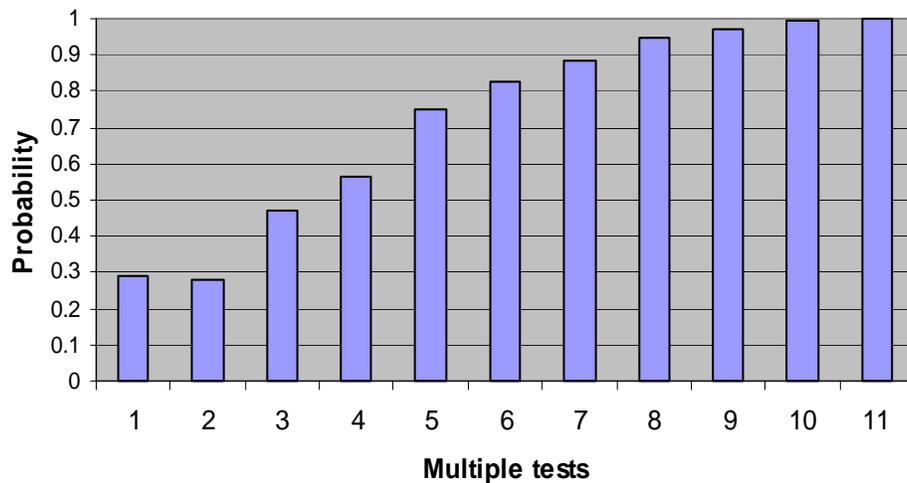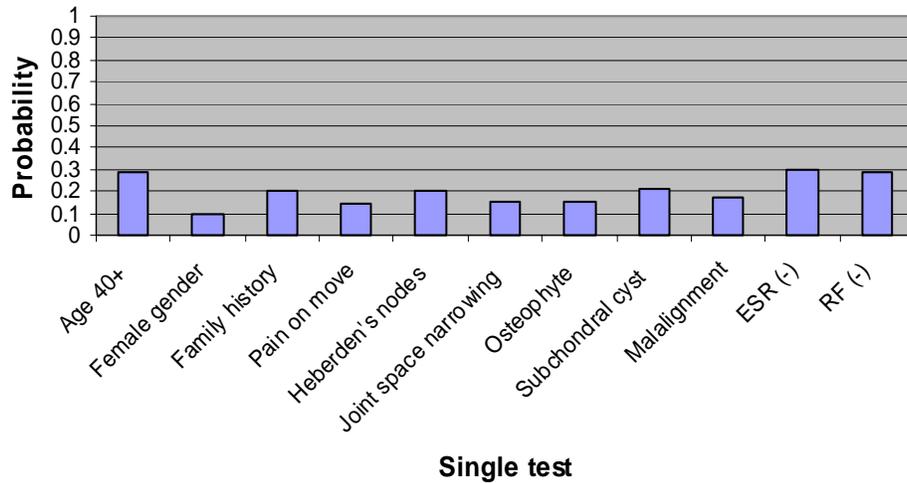
Composite 1:   Age > 40 yrs

Composite 2:   Age > 40 yrs and female gender

Composite 3:   Age > 40 yrs, female gender and family history

Composite 4:   Age > 40 yrs, female gender, family history and pain on move

Composite 5:   Age > 40 yrs, female gender, family history, pain on move and Heberden's nodes

Composite 6:   Age > 40 yrs, female gender, family history, pain on move, Heberden's nodes and joint space narrowing

Composite 7:   Age > 40 yrs, female gender, family history, pain on move, Heberden's nodes, joint space narrowing and osteophytes

Composite 8:   Age > 40 yrs, female gender, family history, pain on move, Heberden's nodes, joint space narrowing, osteophytes and subchondral cysts

Composite 9:   Age > 40 yrs, female gender, family history, pain on move, Heberden's nodes, joint space narrowing, osteophytes, subchondral cysts and malalignment

Composite 10:   Age > 40 yrs, female gender, family history, pain on move, Heberden's nodes, joint space narrowing, osteophytes, subchondral cysts, malalignment and ESR (-)

Composite 11:   Age >40 yrs, female gender, family history, pain on move, Heberden's nodes, joint space narrowing, osteophytes, subchondral cysts, malalignment, ESR (-) and RF (-)
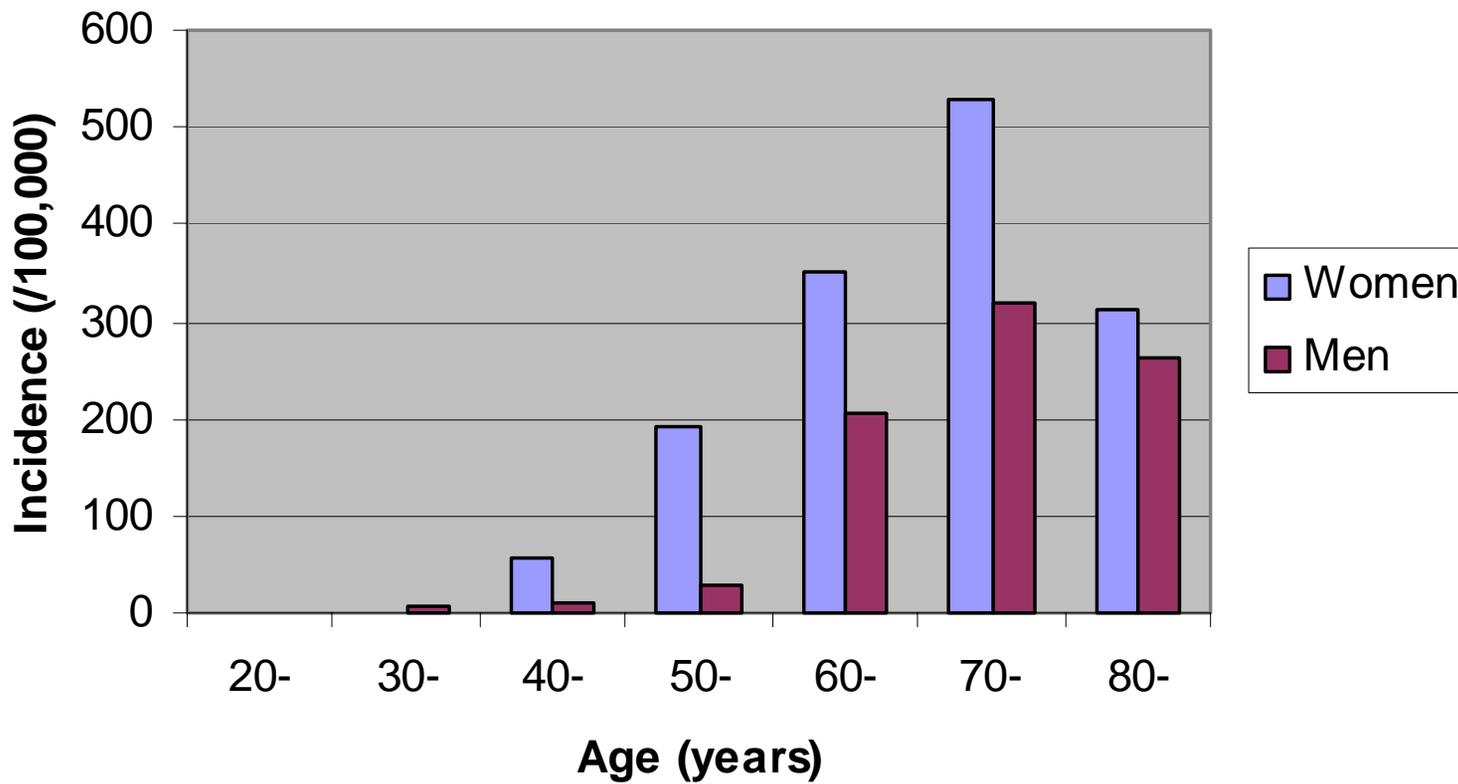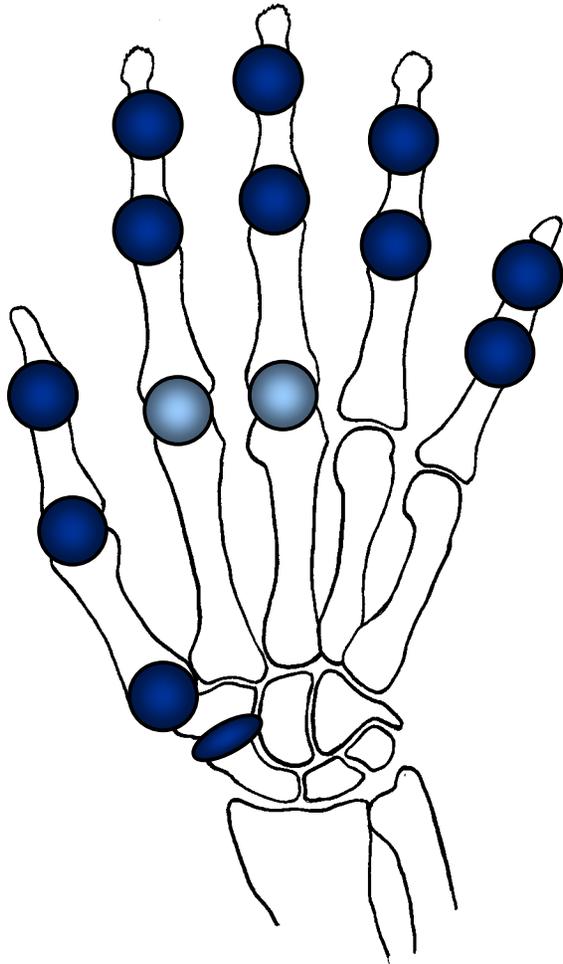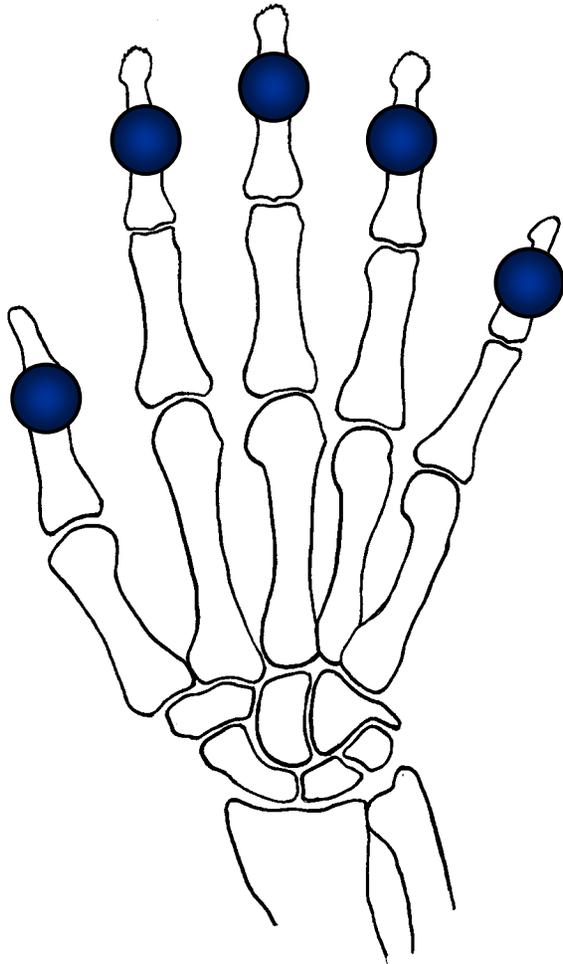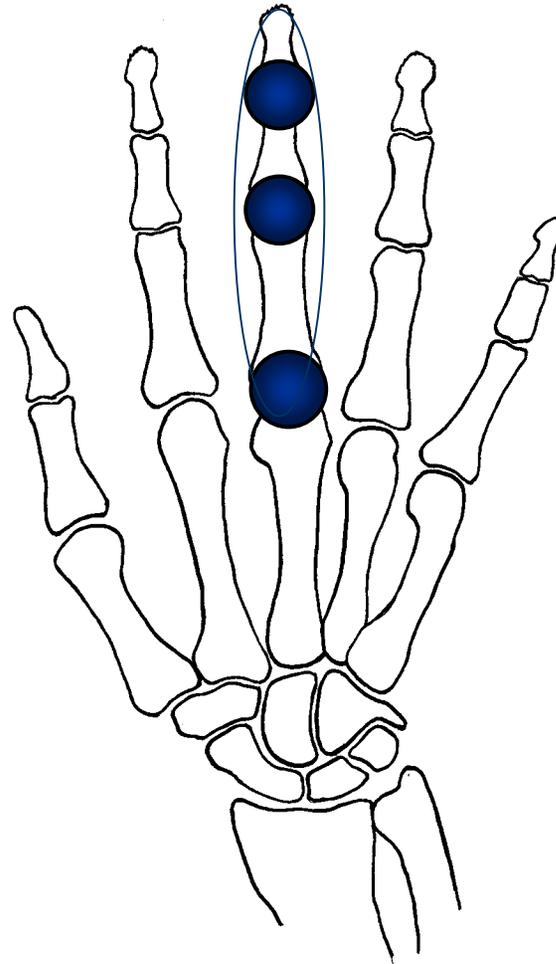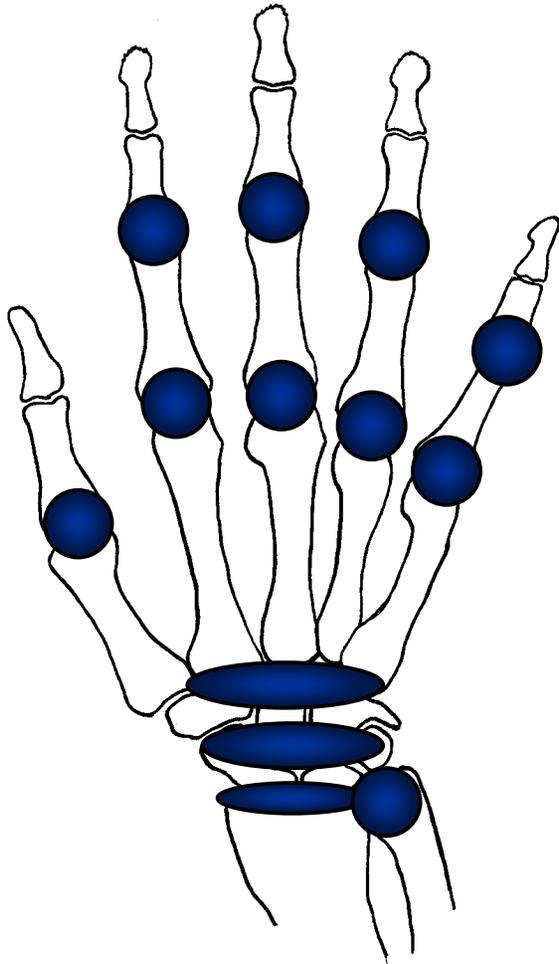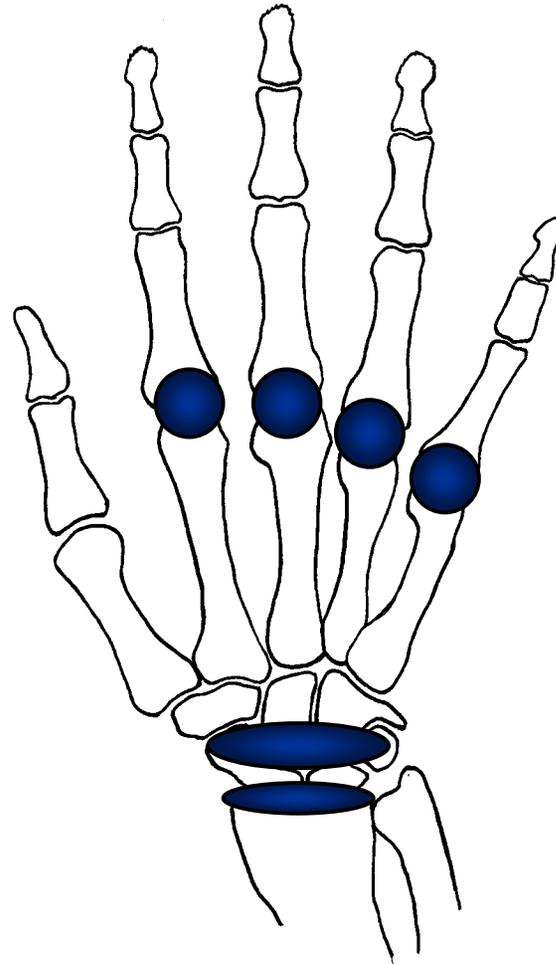
Hand OA
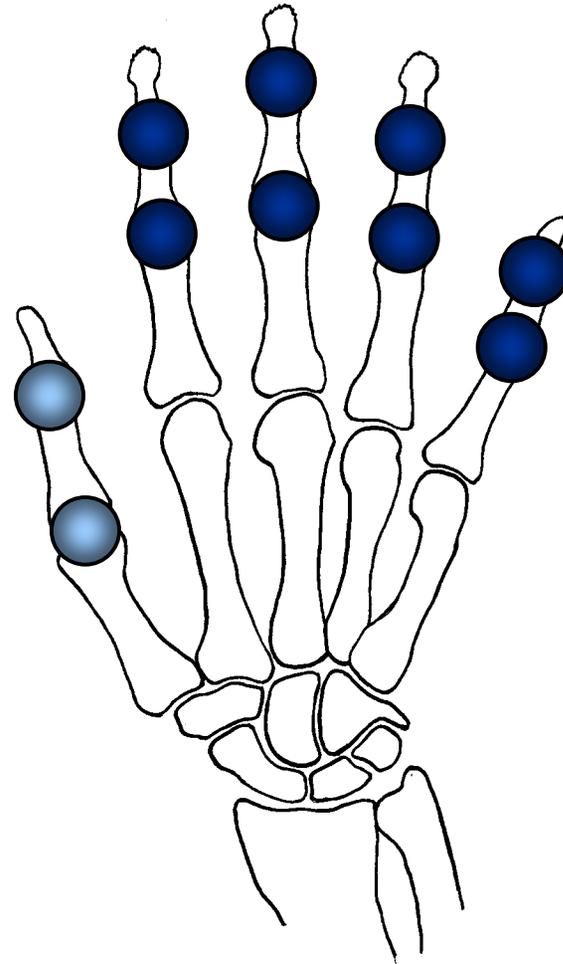
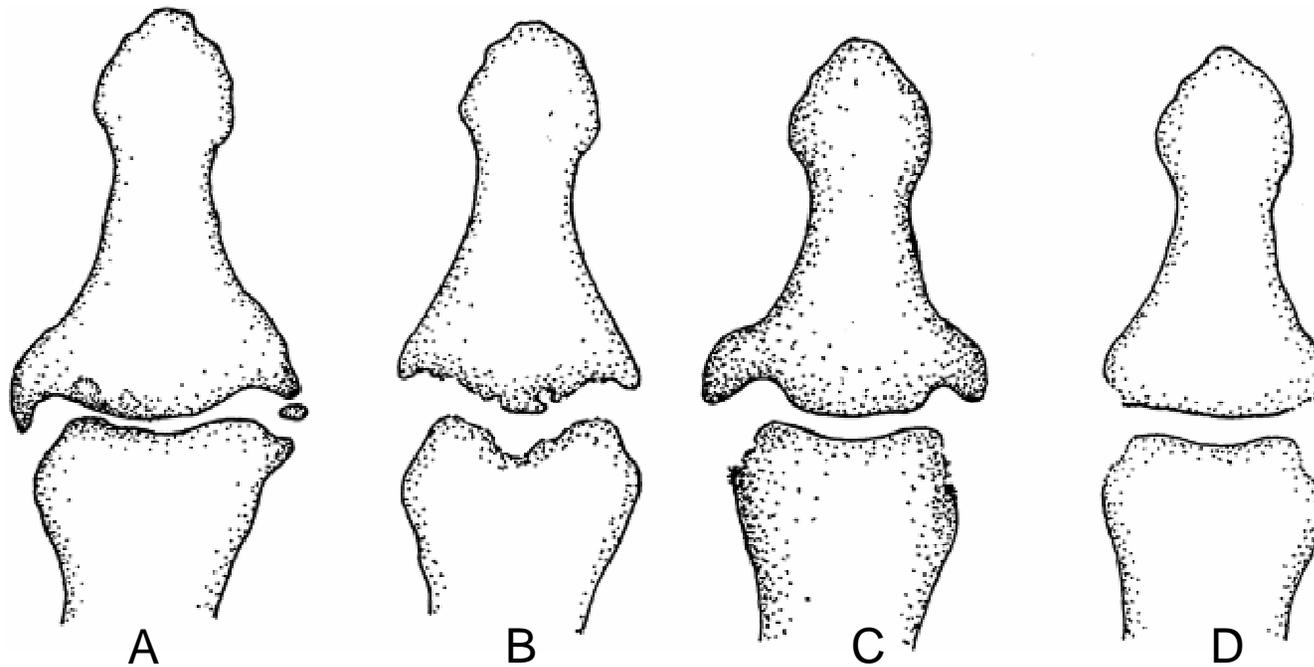Erosive OA

Psoriatic arthritis –
DIPJ pattern

Psoriatic arthritis – dactylitis pattern
(arthritis, osteitis, adjacent peri-
articular inflammation)

Rheumatoid arthritis   Haemochromatosis

Contrasting radiographic features at IPJs of: (A) OA - focal narrowing, marginal osteophyte, sclerosis, osteochondral bodies; (B) erosive OA - subchondral erosion; (C) psoriasis - proliferative marginal erosion, retained or increased bone density; and (D) rheumatoid arthritis – non-proliferative marginal erosion, osteopenia.